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Sir:

Transmitted herewith for filing is the patent application of

Inventor: W. James Huang, Douglas B. Johns and Richard L. Kronenthal

For : IONICALLY CROSSLINKED CARBOXYL-CONTAINING POLYSACCHARIDES FOR ADHESION PREVENTION

Enclosed are:

[ ] _____ sheets of drawing ( ).

[x] Declaration and Power of Attorney (unsigned).

[ ] An assignment of the invention to _____. Assignment Cover Sheet is attached to the Assignment.

[ ] A certified copy of a _____ application.

[ ] Associate Power of Attorney.

[x] Information Disclosure Statement.

[x] One stamped, self-addressed postcard for the PTO Mail Room date stamp.

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IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

Applicant : W. James Huang, Douglas B. Johns and Richard L. Kronenthal

For : **IONICALLY CROSSLINKED CARBOXYL-CONTAINING POLYSACCHARIDES FOR ADHESION PREVENTION**

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I hereby certify that this complete application, including specification pages and claims, is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patent and Trademarks, Washington, D.C. 20231.

A Combined Declaration and Power of Attorney will be submitted to the United States Patent and Trademark Office upon receipt of the U.S. Serial Number for this patent application.

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Eth - 966

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(54) Pharmacological Preparation Based on a Hyaluronic Acid Derivative

(57) The invention relates to a pharmacological preparation for use in human and veterinary medicine. The essence of the preparation contains 0.02 to 3 wt% of an alkali metal hyaluronate complexed with a multivalent cation selected from the group consisting of Mg^{2+}, Ca^{2+}, Zn^{2+}, Ba^{2+}, Al^{3+}, Cu^{2+}, Zr^{4+}, Cr^{3+}, Fe^{3+}, either alone or mixed with physiological salt solution, where the molar composition of the complex is 0.1 to 5 moles of hyaluronate and 1 to 25 moles of the coordinated cation.

The invention relates to a pharmacological preparation based on a derivative of hyaluronic acid that can be used in human and veterinary medicine.

Hyaluronic acid is one of the naturally occurring highly polar polysaccharides known as glycosaminoglycans formerly termed polysaccharides. It is found in skin, tendons, vitreous humor of the eye, synovial fluid in joint capsules, in the cell membranes of certain microorganisms, and the like. Its chemical structure is characterized by alternating saccharide units of 1-3 glucuronic acid and 1-4 acetylglycosamine forming a macromolecular chain with a molecular weight ranging from 300,000 to 8,000,000 or higher.

Pharmacological preparations containing isolated fractions of hyaluronic acid, primarily in the form of its sodium salt, are used in treating inflammatory and degenerative diseases of the joints in humans (e.g., Namiki, Toyoshima, Morisaki, 1982, Clinical Orthopedy, 80, 25-32), or in farm animals (e.g. Asheim, Lindbald, 1976, Acta Veterinarea Scandinavia, 17, 379-394).

A further area of application is in preventing postoperative adhesion of tendons and conjunctival sacs (e.g., Onge, Weiss, Delinger, Balasz, 1980, Clinical Orthopedy, 146, 260-275) and in the treatment of purulent wounds (e.g., Rydell, 1970, Acta Orthopedica Scandinavica, 41, 307-311).

Recently, ophthamalic surgery has become an important area of application of hyaluronates; their use in lens replacement and as a protective medium in corneal transplants, or the implantation of intracameral lenses, and elsewhere (e.g., Balasz, Pape, 1980, Ophthalmology, 87, 699-705).

The drugs used heretofore contain hyaluronic acid in purified form, most frequently as its sodium salt in physiological salt solution. An example is HEALON manufactured by Pharmacie in Sweden. Other preparations include Hyvisc (Med-Chem Products, Inc., Boston, Mass.), which contain hyaluronate sodium, or preparations based on a combination of hyaluronic acid and keratan sulfates or heparan sulfate, or preparations with other glycosamino-glycans manufactured under different commercial names, such as Arteparon, Reparan, etc.

The effectiveness of drugs based on acid mucosaccharides is ordinarily directly proportional to their specific molecular weight; drugs of higher molecular weight can be administered in lower concentrations, and their physiological effectiveness is generally greater. In the case of molecular weights lower than 1.5 million, these drugs have to be administered in fairly large doses, which may cause problems as the function of the eye returns to its original physiological state.

This disadvantage is essentially eliminated by the pharmacological preparation in accordance with the invention, which consists essentially in that it contains 0.02 to 3 wt% of a complex of a hyaluronate of an alkali metal with a multivalent cation selected from the group Mg^{2+}, Ca^{2+}, Zn^{2+}, Ba^{2+}, Al^{3+}, Cu^{2+}, Zr^{4+}, Cr^{3+}, Fe^{3+}, alone or in a mixture with physiological salt solution, where the molar composition of the complex is 0.1 to 5 moles of the hyaluronate to 1 to 25 moles of the coordinated cation. In

this preparation the active ingredient is a complex compound in which isolated molecules of hyaluronic acid, most frequently but not exclusively in the form of its sodium salt, are bound in pairs or larger groups by a coordinate bond to the carboxyl groups of the hyaluronate and by cations of multivalent bases such as Mg^{2+}, Ca^{2+}, Al^{3+}, Zn^{2+}, or others.

The resulting dimer, trimer, or higher-order complex compounds retain the properties of hyaluronic acid, but when the molecular weight increases by a factor of two or more, solutions of it become more thixotropic and exhibit higher viscosity and gel strength than isolated hyaluronic acid.

The dimerization can be accomplished by adding salts of multivalent cations or hydroxides of these multivalent metals to an aqueous solution of hyaluronic acid or the hyaluronate of an alkali metal. Because coordination bonds are stronger than the ionic bonds of alkali metals such as Na^{+} or K^{+}, the cations of the carboxyl group are displaced almost quantitatively, and the bond of the multifunctional coordinated group enables pairs of hyaluronate molecular chains to form, bound by a relatively strong complex bond. In complexes containing cations capable of olefication or oxalation* (Al^{3+}, $Zr^{4}+$, Cr^{3+}, etc.), the polyfunctionality of the central atom becomes even higher, e.g. the coordination number of Al^{3+} is 6, that of $Zr^{4}+$ is 8, and the carboxyl group of the glucuronic saccharide unit can be bound by a one- or two-donor ligand.

In the relatively complicated purification procedures used in preparing isolated hyaluronic acid derivatives there is the risk of depolymerization, which is supported by oxygen and catalyzed by heavy metals. Depolymerization is also caused by heavy metals from tissue (primarily from ferrohemoglobulin), and protective measures must therefore be taken during extraction (chelating agent, nitrogen atmosphere).

On the other hand, once the drug is prepared and no longer being vigorously stirred and is stored in the dark, the addition of heavy metals is not as deleterious. The approximately equimolar quantity used ensures complexing of the metals (which is the same as the addition of chelaton) by the hyaluronic carboxyl group, that is, it ensures they are "masked" and cannot catalyze depolymer-ization. This is also shown by their good stability: they have a storage life of at least one year for preparations according to the invention when stored in the dark at a fairly low temperature.

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*Translator's note: Literally translated from the Slovak.

Example 1

In apyrogenic distilled water, 10 mg of hyaluronic acid in the form of its sodium salt is dissolved at room temperature, 0.2 mg of $MgCl_2 \cdot 6H_2O$ is added, and after it dissolves, 8.5 mg of NaCl, 0.28 mg of $Na_2HPO_4 \cdot H_2O$, and 0.04 mg of NaH_2PO_4 are added and the solution is made up to a volume of 1 ml. This preparation is suitable for use in ophthamalic surgery.

Example 2

In 1 ml of apyrogenic physiological salt solution, 15 mg of a complexed dimer of hyaluronate sodium containing on average 1 mole of Al^{3+} per every two moles of hyaluronate sodium is dissolved at room temperature. The preparation is suitable for use in joint surgery and for other pharmacological purposes.

Example 3

In 1 ml of apyrogenic physiological salt solution 10 mg of a complex compound of hyaluronic acid containing 1 mole of Ca^{2+} to every 1.5 moles of hyaluronic acid is dissolved at room temperature. The preparation is of general utility in human and veterinary medicine.

Example 4

In 1 ml of apyrogenic physiological salt solution 6 mg of NaCl and 10 mg of a complex compound with the composition of 1 mole of Cr^{3+} and 2 moles of hyaluronate sodium are dissolved at room temperature.

Example 5

An aqueous solution is made up by dissolving 10 mg of hyaluronate sodium and 0.001 mg of $ZnSO_4 \cdot 7H_2O$ in 10 ml of apyrogenic physiological salt solution.

Example 6

An aqueous solution is made up by dissolving 10 mg of hyaluronate sodium and 0.0005 mg of $Zr(SO_4)_2$ in 5 ml of apyrogenic physiological salt solution.

Claim

A pharmacological preparation based on a derivative of hyaluronic acid that can be used in human and veterinary medicine, characterized in that it contains 0.02 to 3 wt% of an alkali metal hyaluronate complexed with a multivalent cation selected from the group consisting of Mg^{2+}, Ca^{2+}, Zn^{2+}, Ba^{2+}, Al^{3+}, Cu^{2+}, Zr^{4+}, Cr^{3+}, Fe^{3+}, either alone or mixed with physiological salt solution, where the molar composition of the complex is 0.1 to 5 moles of hyaluronate per 1 to 25 moles of the coordinated cation.